UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
REGION 8
1595 Wynkoop Street
DENVER, CO 80202-1129
Phone 800-227-8917
http://www.epa.gov/region08

January 3, 2011

Ref: 8P-W

MEMORANDUM

SUBJECT: Peer Review of ATSDR's Health Consultation on Sulfolane

FROM: Robert Benson, Ph.D.
Toxicologist, Water Program

TO: James Holler, Acting Director
Division of Toxicology and Environmental Medicine
US Agency for Toxic Substances and Disease Registry

As you requested I reviewed the materials on sulfolane. My responses to the questions follow.

Question 1. Did ATSDR select the appropriate point of departure in its assessment of sulfolane?

I agree with using Zhu et al. (1987) as the principal study as it provides information on an adverse health effect (fatty liver) at the longest duration (6 months) in the most sensitive species (guinea pig). I also agree that 2.5 mg/kg-day is a NOAEL and that 25 mg/kg-day is a minimal LOAEL. As described below I would choose an alternative procedure for doing the exposure-response relationship and would also use a different uncertainty factor for subchronic to chronic exposure.

Question 2. Are the methodologies used to establish the provisional health guidance value for sulfolane by ATSDR scientifically sound and sufficiently protective of public health?

The procedures used in the Health Consultation conform to ATSDR's practices when using the NOAEL/LOAEL approach to derive the Minimal Risk Level. However, ATSDR usually does not use an uncertainty factor for to derive a chronic MRL from a subchronic MRL. The usual practice is to derive a subchronic MRL from a subchronic study and not derive a chronic MRL when a chronic study is not available. However, I do believe that using the 10-fold uncertainty factor to derive the provisional health guidance value is protective of public health.

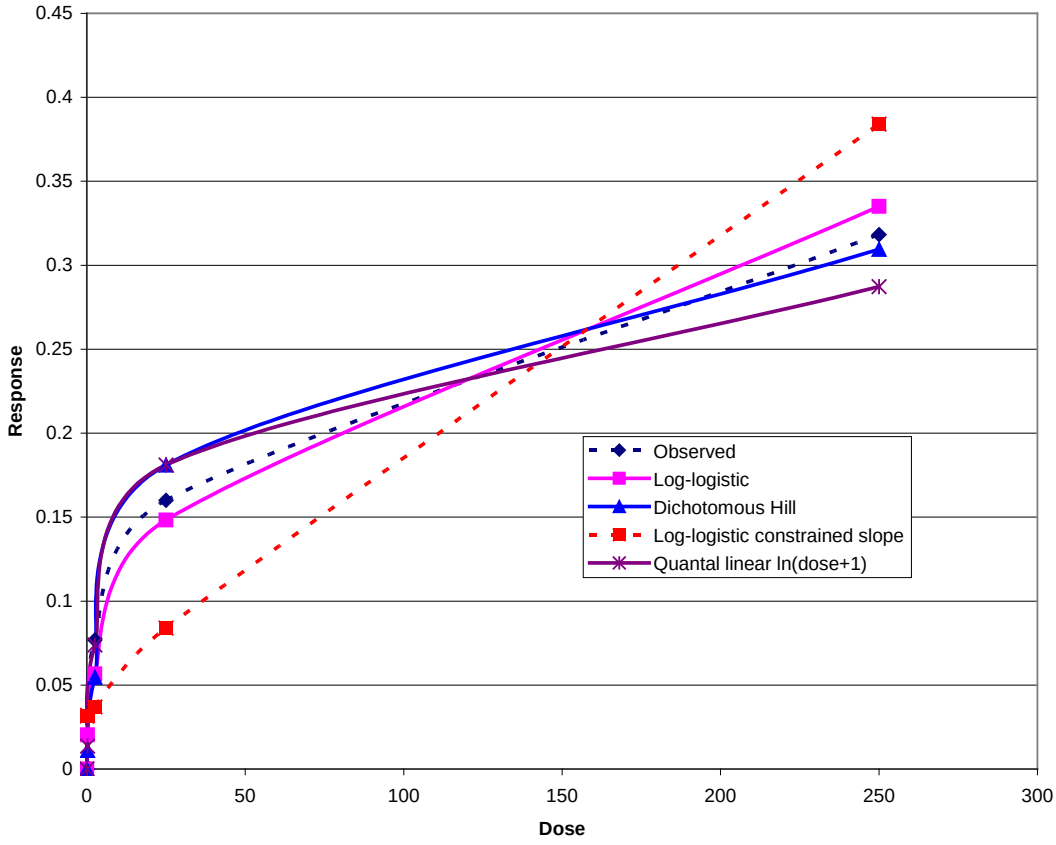
My view is that the 10-fold uncertainty factor for fatty liver is more than is warranted in this case. I recommend using a 3-fold uncertainty factor to derive the chronic value.

Question 3. Is the slope-restricted log-logistic BMDS of the Zhu et al. 1987 guinea pig fatty liver degeneration overly anti-conservative?

Figure 2 in the Health Consultation shows that the slope-restricted log logistic model provides a poor visual fit to the observed data. I believe ATSDR's decision to reject this model is appropriate.

Question 4: Is the log transformed quantal-linear model of the Zhu et al. 1987 guinea pig liver data scientifically sound? Is the resulting BMDL preferable to the BMDL from the slope-restricted log logistic model of the same data?

While the log transformed quantal-linear model is scientifically sound, I prefer an approach not requiring log transformation. EPA's benchmark dose software (version 2.1.2) provides the option of running the log-logistic model with the slope unconstrained. In addition the software contains the Dichotomous Hill (a log-logistic model that allows the plateau to be less than 1). The results of these models are plotted in the following figure.



The log-logistic model with unconstrained slope, the Dichotomous Hill model with unconstrained slope, and the Quantal linear ln(dose+1) model fit the observed data much better than the log-logistic model with constrained slope. BMD_{10} and $BMDL_{10}$ values for these three models are provided in the table below. However, there is no practical difference in the results of the three models.

Model	**BMD_{10}**	**$BMDL_{10}$**
Log-logistic unconstrained slope	9.45	1.21
Dichotomous Hill unconstrained slope	6.94	1.34
Quantal linear ln(dose+1)	4.58	2.07

Question 5. Are the health consultation's results presented and interpreted appropriately and completely?

See the responses to Question 1, 2, and 4.

Question 6. Are the health consultation's conclusions and recommendations appropriate and complete?

I agree that the chronic value of 0.0025 mg/kg-day is protective of public health. However, I would use a different procedure for the exposure-response characterization and a lower total uncertainty factor to give a higher action level. I would use the $BMDL_{10}$ for the log-logistic model with unconstrained slope and a total uncertainty factor of 300 (10 each for interspecies and intraspecies extrapolation and 3 for subchronic to chronic) to give a value of 0.004 mg/kg-day (1.21/300, rounded to 1 significant digit).

Question 7. Are there any notable omissions or ambiguities in scientific logic anywhere in the health consultation that would be germane to the evaluation of potential adverse health effects?

I would caution against comparing the concentration of sulfolane in the drinking water to the values listed at the top of page 2 calculated with the child-specific intake factors and the chronic value of 0.0025 mg/kg-day. The calculated increased exposure for children will not occur for a lifetime.

Question 8. Are there any other comments on the health consultation?

There are several editorial changes I recommend before the Health Consultation is released.

Page 2. The ToxStrategies report is dated 2010.

Page 2. The ToxStrategies reference dose is 0.02 mg/kg-day.

Page 3. In the discussion of the Fishers Exact test, I recommend using a term different from "conservative."

Page 3, 1. Delete the "in" after "that" in line 1.

Page 3. In the Alternative BMDL Approaches paragraph, I recommend using a term different from "anti-conservative."

Page 12, top of page. LOAEL is Lowest Observed Adverse Effect Level

Page 12, Table 4. ToxStrategies used an Uncertainty Factor of 3 for both S and D.